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Differential brain effects of laser and needle acupuncture at LR8 using functional MRI

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ABSTRACT

Objective While needle acupuncture is a well-accepted technique, laser acupuncture is being increasingly used in clinical practice. The differential effects of the two techniques are of interest. We examine this in relation to brain effects of activation of LR8, a putative acupuncture point for depression, using functional MRI (fMRI).

Methods Sixteen healthy participants were randomised to receive low intensity laser acupuncture to LR8 on one side and needle acupuncture to the contralateral LR8. Stimulation was in an on-off block design and brain patterns were recorded under fMRI.

Results Significant activation occurred in the left precuneus during laser acupuncture compared with needle acupuncture and significant activation occurred in the left precentral gyrus during needle acupuncture compared with laser acupuncture.

Conclusions Laser and needle acupuncture at LR8 in healthy participants produced different brain patterns. Laser acupuncture activated the precuneus relevant to mood in the posterior default mode network while needle acupuncture activated the parietal cortical region associated with the primary motor cortex. Further investigations are warranted to evaluate the clinical relevance of these effects.

INTRODUCTION

Acupuncture is a popular form of complementary medical intervention used to treat a number of disorders including neuropsychiatric illnesses.^{1–8} The traditional modality of acupuncture has been with needles applied manually. A number of investigators have examined the possible mechanisms by which needle acupuncture (NA) may produce physiological effects, with many neural structures being implicated including peripheral nerves, neurovascular bundles,

mechanoreceptors, nerve endings and neuromuscular attachments.^{9–18}

In the 1970s, with the advent of laser technology, low intensity laser acupuncture (LA) emerged as a new modality of acupuncture and increased in popularity. The main advantages of LA were that it was painless and infection-free because there was no needle puncture. It was also easy to deliver, making it time-efficient and cost-effective. Because of the lack of any skin sensation, low intensity laser was also easy to blind in any experimental design, making it an ideal research tool. In spite of these qualities and its increasing clinical importance, there is a dearth of investigations into its neurophysiological effects and clinical efficacy.^{19–21} Little is known about the peripheral pathways and spinal and central mechanisms involved in LA.

The application of functional MRI (fMRI) to acupuncture research has opened up an avenue to investigate the CNS effects of the various modalities of acupuncture.^{22–34} In our previous studies, fMRI was used to examine the brain response to LA on four acupuncture points (LR8, LR14, CV14 and HT7) in both healthy participants and those with depression.^{35,36} The choice of acupuncture points in the fMRI studies was based on a pilot clinical study to demonstrate the effectiveness of a suite of acupuncture points in the treatment of mild to moderate depression in primary care,⁸ with LR8 stimulation having produced the most salient effect. These studies showed that the brain activation patterns in depression during LA were different from those in healthy participants, with a significant shift from the frontolimbic cortices to the parieto-temporal-cerebellar regions in those with depression. Another



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network of interest found with the brain effects of acupuncture is the default mode network (DMN),³⁷³⁸ also known as the resting state network. The DMN is active when the brain is not involved in any specific task. When the DMN is active, self-referential activity occurs in the resting brain as part of its preparation before the next task.³⁷³⁸ This self-referential activity is associated with the 'sense of self' important in the well-being of the individual.

In this study we chose LR8 (which produced the most salient antidepressant effect in our previous work) to compare the brain effects of the two modalities (LA vs NA) in healthy individuals. We also wanted to record their impact on the DMN.

METHODS

Recruitment

Sixteen healthy individuals (eight women and eight men) aged 18–60 years (mean 48.2 years) were recruited by advertisement through the University of New South Wales, Black Dog Institute and a private medical acupuncture clinic in Sydney.

Study design

Each participant received LA on the medial knee acupuncture point LR8 (at the junction of the semitendinosus and semimembranosus tendon insertion site above the knee) and NA at LR8 on the other leg, with the side of stimulation being counterbalanced across the group; in other words, for the whole sample there was equivalent left- and right-sided stimulation with NA and LA.

During the fMRI scan, two runs were used for either LA or NA condition in randomised order. Each run had alternating rest/active phases, beginning with a rest phase, and consisted of 17 blocks with eight active phases (block) alternating with nine rest phases (block). The duration of each active block was 20 s, including 2 s preparation time, 16 s of continuous acupuncture stimulation and 2 s of repetition time (TR) at the end for the scanner to pick up the BOLD signal. The rest block was set at 20 s to match the active block. Both laser stimulation and needle stimulation were time-locked to signalling.

Inclusion criteria

Participants were right-handed, had no history of significant medical or psychiatric disorder, were not currently on any medication other than vitamin supplements, had no contraindications to an MRI scan and provided written informed consent.

Exclusion criteria

Exclusion criteria included ongoing uncontrolled systemic illness, acute illness, brain injury, past surgery involving the lower limbs and any contraindications to MRI (pacemaker, ferromagnetic implants or foreign body, claustrophobia).

Withdrawal criteria

Subjects were withdrawn if any of the abovementioned exclusion criteria occurred in the interim before the procedure or if the subject became agitated or anxious during the procedure.

Randomisation and blinding

Randomisation has been described above in the study design. There was no blinding of either the participant or the acupuncturist. The block (rest/active) design accommodated for the placebo response to both needle and laser stimulation.

INTERVENTION

Practitioner background

LA and NA were conducted by IQ-S and TL. IQ-S is a Fellow of the Australian Medical Acupuncture College (AMAC) and has been a clinical acupuncturist for 20 years. TL has expertise in integrative neurophysiology and is a rehabilitation medicine specialist.

The needle

Single usage Helio-sourced non-ferrous silver needles with dimensions 0.22 mm×25 mm, which are compatible with the magnet, were used. The location of LR8 was confirmed by anatomical landmarks and needle puncture was followed by rotation in 1 Hz cycles in a 45 degrees clockwise direction to produce the *de qi* sensation typical of manual acupuncture while undergoing MRI acquisition. The needling blocks were achieved with time-lock to signalling for MRI acquisition.

The laser

A Moxla prototype fibrooptic infrared light laser (Euryphaessa AB, Stockholm, Sweden), 808 nm with 20 mW capacity and a fibrooptic arm was developed for use in the scanning room. Location was confirmed by anatomical location. A stably-held laser was applied to the skin by the acupuncturist for the duration of the laser session according to the time signal. The switching on and off was achieved with a computer signal time-locked to the MRI acquisition.

Sensory stimulation reporting

After the acupuncture intervention under fMRI acquisition the participants were each asked to assess the sensory stimulation they underwent; the sensory descriptions were light touch, pressure, fullness, heaviness, ache, soreness, numbness, tingling, warmth, pain and 'other'.

FMRI

Imaging was performed on a 3T Philips Intera MRI scanner (Philips Medical Systems, Best, The Netherlands) for both T1-weighted three-dimensional (3D) structural and BOLD contrast functional MRI. The 3D structural MRI was acquired in sagittal orientation

using a T1-weighted TFE sequence (TR/TE=6.39/2.9 ms; flip angle=8; matrix size=256×256; FOV=256×256 mm; slice thickness 1.0 mm), yielding sagittal slices of 1.0 mm thick and an in-plane spatial resolution of 1.0×1.0 mm, producing an isotropic voxel of 1.0×1.0×1.0 mm. A gradient echo-planar imaging (EPI) technique (TR/TE=2000/40 ms; matrix size=128×128; FOV=250×250 mm; in-plane pixel size 1.953×1.953 mm) was used to acquire T2-weighted BOLD contrast fMRI in axial orientation. The whole brain was covered using 21 slices at 5.0 mm slice thickness.

Image preprocessing

Imaging data were analysed using statistical parametric mapping (SPM2, Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab V6 (The Mathworks). All volumes were realigned spatially to the first volume and the time series for voxels within each slice realigned temporally to acquisition of the middle slice. Resulting volumes were normalised to a standard EPI template based on the MNI. The normalised images were smoothed with an isotropic 8 mm full-width half-maximal Gaussian kernel. The time series in each voxel was highpass filtered to 1/120 Hz to remove low-frequency noise.

Image postprocessing

Statistical analysis was performed in two stages assuming a random effects design. Each stimulation site was compared with the rest condition for first-level analysis. The BOLD response to the acupuncture stimulation was modelled by a canonical haemodynamic response function (HRF).

Half the participants' images were flipped and the group was then processed as a whole under second-level analysis (ANOVA) at the whole brain level. Each individual participant's contrast images, which were effectively the statistical parametric maps of the t-statistics for each voxel from the first-level analysis, were put into this second-level design. We used a one-sample t test to examine the activation pattern of each acupuncture group and a within-subject two-sample t test to compare the activation differences between the two types of acupuncture. To correct for multiple comparisons, areas with a p value<0.05 following cluster-level Family Wise Error (FWE) correction were considered significant, with an initial uncorrected p value threshold of <0.001 and the extent threshold to 15 contiguous voxels.

RESULTS

First-level analysis

NA at LR8 showed increased activation at the right insula ($p_{\text{FWE}}=0.001$) and left precentral gyrus and insula ($p_{\text{FWE}}<0.001$) (figure 1, table 1). There was also deactivation at the left precuneus ($p_{\text{FWE}}=0.002$). No significant results were found for LA acupuncture

at LR8, indicating that there was no consistent activation or deactivation at the first level.

Second-level analysis

When the activation patterns for LA and NA were compared, NA produced greater activation in the left precentral gyrus ($p_{\text{FWE}}=0.023$) and LA produced more activation in the left precuneus ($p_{\text{FWE}}=0.003$) (figure 2, table 2).

Sensory stimulation: laser versus needle

All participants felt the touch of the laser probe but only a few reported any sensation produced by the laser beam itself, with three reporting a tingling sensation, one a feeling of warmth and one reporting both these sensations. Needle acupuncture with *de qi* produced more sensory changes, with all participants reporting pressure and tingling and three reporting pain (see online appendix, supplementary tables S1 and S2).

Adverse effects: laser and needle acupuncture, MRI experience

On a scale of 0 (none) to 6 (severe), mean scores of adverse effects with LA were: transient tiredness and dizziness (0.13), vagueness (0.125) and nausea (0.06). Adverse effects with NA were: pain (0.50) and unwell (0.13). The MRI experience caused mild discomfort (0.44) and anxiety (0.44) (see online appendix, supplementary table S3).

DISCUSSION

Functional MRI studies with NA have indicated that deactivation of the limbic-paralimbic-neocortical network and activation of the somatosensory cortex are involved during NA intervention. Deactivation of the limbic system occurs with correct *de qi* needling technique, whereas poor technique resulting in the pain sensation causes the opposite reaction (activation of the limbic system). Some of the limbic-paralimbic regions were identifiable as being part of the DMN.^{12 13 22 23} These studies have selected acupuncture points which are clinically known to be uncomfortable when *de qi* needling is applied (eg, LI4 and ST36). The insula is involved in NA and our first-level findings confirmed those in the literature.^{12 13 27-34} The limited literature on the brain effects of LA suggests limbic-paralimbic-neocortical activation but no significant activation of the somatosensory cortex.^{20 21} Ipsilateral brain activation was also observed. One study on healthy participants reported that this ipsilaterality was only seen with limb acupuncture points and not truncal acupuncture points.³⁵ The ipsilaterality suggests the involvement of the autonomic nervous system in LA mechanisms of action. There was no significant activation or deactivation of the somatosensory cortex, with the low intensity laser stimulation being free of pain or ache. This may contribute to the

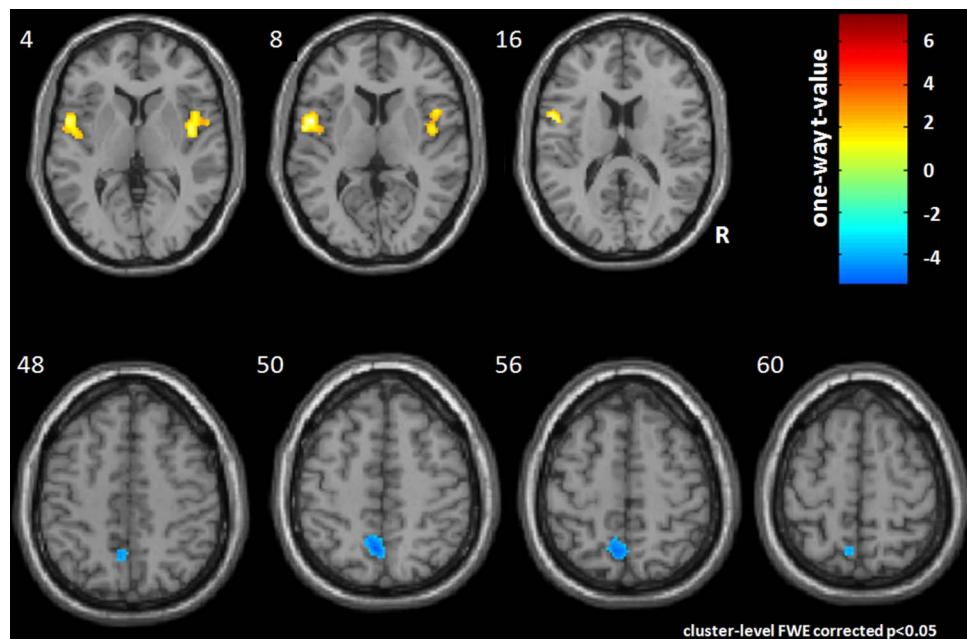


Figure 1 A one-sample t test was used to show the activation pattern of needle acupuncture. Significant activation ($p<0.05$) corrected (Family Wise Error) was found at the bilateral insula and left precentral gyrus as well as deactivation at the left precuneus.

interindividual variability in the first-level analysis with LA while first-level analysis with NA demonstrated significant activation of the insula, important in pain pathways and deactivation of the posterior DMN. Unlike previous NA studies reporting somatosensory cortical changes, the precentral gyrus linked to the primary motor cortex was activated. The above literature therefore suggests that the NA and LA acupuncture afferent pathways may be different, the former due to its somatosensory and sensorimotor input following afferent pain pathways^{9 10} and the latter possibly more autonomically driven.^{19 35 36}

The literature shows that both NA and LA modulate the DMN. The DMN is a composite of brain regions activated when the brain is at rest and not involved in an active task. It is therefore also referred to as the task negative brain network. During DMN time the healthy individual reflects on his or her life and his or her hopes and aspirations.³⁹ It may be that activation of the DMN is responsible for the feeling of well-being from acupuncture intervention. Some may

argue the case that the well-being is from the placebo effect. The DMN may be an integral part of every acupuncture intervention, directly contributing to the maintenance of 'sense of self' and well-being.^{37 40}

The posterior DMN is important in depression.⁴⁰⁴¹ LR8 is the most important acupuncture point in the LA treatment regime for depression that was tested in our previous work.³⁵ The significant activation of the left precuneus (as part of the posterior DMN) after FWE correction when LA is applied to LR8 across the group in the second-level analysis is further confirmation of the clinical efficacy of LA in depression.⁸ In NA, deactivation of the left precuneus was noted at the first-level analysis, confirming the deactivation of this part of the posterior DMN. This could be part of an antidepressant effect of NA at LR8. Further needle fMRI acupuncture studies are needed to confirm the efficacy of this acupuncture point in depression.

In the first-and second-level analyses, measuring activation less than or greater than a baseline (in this case, rest) are referred to as deactivation and

Table 1 First-level analysis relative to resting state: significant results for NA

	k	p _{FWE}	Regions	MNI coordinates			
				x	y	z	T
Activation							
Cluster 1	426	<0.001	L insula L precentral gyrus	-54 -48	4 2	10 18	7.29 5.86
Cluster 2	229	0.001	R insula	44	-6	6	6.12
Deactivation							
Cluster 3	197	0.002	L precuneus	-4	-52	54	

FWE, family wise error; MNI, Montreal Neurological Institute; NA, needle acupuncture; T, T value for t-test.

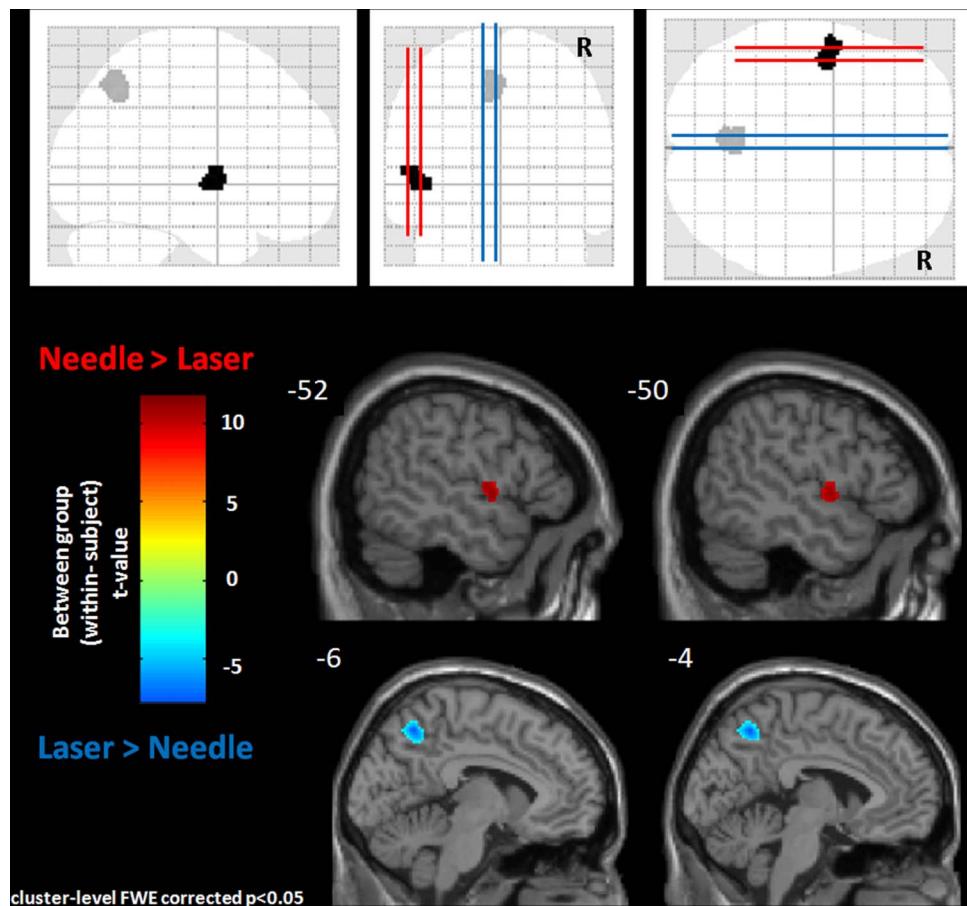


Figure 2 A within-subject t test was used to show differences in activation between needle acupuncture and laser acupuncture. Needle acupuncture activated the left precentral gyrus while laser acupuncture activated the left precuneus. All the results have been corrected for multiple comparison error.

activation, respectively. However, in this study, for second-level analysis, deactivation is impossible to interpret as we are subtracting two tasks from each other (NA vs LA) and not comparing them with rest. We found that NA significantly stimulated the left precentral gyrus compared with LA, and the latter significantly activated the left precuneus compared with the former. It is not known why the left precentral gyrus in NA and the left precuneus in LA are stimulated for these modalities in this comparison. In the protocol it was ensured that equivalent numbers of left- and right-sided NA and LA were conducted. The left-sidedness may be limited to our sample alone. Further studies may be required to clarify the brain functions

of LR8 when stimulated by different modalities of acupuncture.

Interestingly, in spite of NA at this acupuncture point using the *de qi* method to cause the traditional 'achy' sensation, there was no significant stimulation of the somatosensory cortex (represented as the post-central gyrus). Instead, NA at LR8 produced significant activation at the precentral gyrus after FWE correction. The precentral gyrus is an important region which includes the motor cortical regions⁴² (primary motor or somatomotor cortex and the lateral premotor cortex). Previously, sensorimotor implicated acupuncture points (GB34, GB35, GB39, ST36 on the leg and LI9, LI10, LI13, LI14 on the arm) have

Table 2 Second-level analysis: significant activation differences between NA and LA

Regions	MNI coordinates			k	p _{FWE}	T
	x	y	z			
Needle>laser						
L precentral gyrus	-56	-2	8	119	0.023	4.95
Laser>needle						
L precuneus	-6	-56	44	174	0.003	3.73

FWE, family wise error; LA, laser acupuncture; NA, needle acupuncture.

been shown to increase brain activation of the pre-motor and supplementary motor regions.⁴³ Another study showed that NA at GB34/BL57 caused deactivation of the primary motor cortex and premotor cortex.⁴⁴ The findings of NA at LR8 in this study are only preliminary fMRI evidence. More investigations are warranted to evaluate the role of NA at LR8 in the modulation of motor cortical regions and hence its likely usefulness in motor rehabilitation clinically.

Empirically, LR8 is not particularly uncomfortable or painful when needled to produce the *de qi* sensation, unlike widely investigated acupuncture points ST36 or LI4 which are known to be uncomfortable to similar needling. This observation suggests that maybe not all acupuncture points produce somatosensory changes when needled.¹²⁻²⁵ In the case of LR8, the outcome from this study is that NA at this acupuncture point is significantly somatomotor. In the literature, among its applications, LR8 is empirically used for muscle spasms, pareses and paretic tendencies.⁴⁵ Classically, it is meant to 'benefit the sinews'. It would be interesting to perform further work on other mid lower limb acupuncture points to test their sensorimotor implications.

The sensory signalling (if any) perceived by the participants from LA was light touch (for all participants) and tingling and/or warmth (n=2), and only one participant felt pressure. Warmth being C fibre-linked and light touch and tingling being more so, A- β linked sensations may be part of LA's afferent fibres. Evaluation of the sensory signalling with NA showed that pressure and tingling (n=10) were felt by more participants than light touch (n=6) or ache (n=5). Interestingly, with LA all of the participants felt light touch and only three participants felt anything more than light touch. This may suggest an A- β and possibly non-nociceptive C afferent involvement with LA, whereas NA probably sets up activity in A- β , A- δ and C fibres (nociceptive as well as non-nociceptive).^{9,46} More investigations are warranted to identify definitively the afferent fibre types involved in LA.

There are limitations to these findings. They may be confined to this low intensity laser (808 nm). Although we had 16 participants, this is still a relatively small sample size. This study was conducted on healthy participants and NA or LA at LR8 may produce totally different brain patterns in participants with health problems.

CONCLUSION

NA and LA at LR8 produce different brain patterns, highlighting the differential application of these two modalities of acupuncture. These activation patterns are consistent with the suggestion that LA at LR8 may be useful in the treatment of mood disorders while NA at LR8 may be useful in the modulation of motor cortical regions and hence may have a place in motor

rehabilitation. These are only preliminary findings and further investigations with larger samples are warranted.

Summary points

- ▶ Laser and needle acupuncture at LR8 significantly activated different brain regions.
- ▶ Laser acupuncture activated the precuneus, part of the posterior default mode network.
- ▶ Needle acupuncture activated the precentral gyrus, part of the motor cortical brain regions and not the sensory cortical brain regions.

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Contributors IQ-Sdesigned and managed the study, recruited participants, conducted the laser/needle intervention under fMRI, analysed the data and wrote the manuscript. MW helped with study design and data analysis. TL conducted the laser/needle intervention under fMRI and helped with writing the manuscript. CS analysed the data and helped with writing the manuscript. PS contributed to the study design, ethical application and writing the manuscript.

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Competing interests None.

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Provenance and peer review Not commissioned; internally peer reviewed.

Data sharing statement We are happy to discuss data sharing as approved by the senior author Professor Perminder Sachdev.

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